International Journal of Cardiology 215 (2016) 263–268

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Glycemic variability is an important risk factor for cardiovascular autonomic neuropathy in newly diagnosed type 2 diabetic patients

Wen Xu [a,1,2], Yanhua Zhu [a,1,2], Xubin Yang [a,1,2], Hongrong Deng [a,2], Jinhua Yan [a,2], Shaoda Lin [b,2], Huazhang Yang [c,2], Hong Chen [d,2], Jianping Weng [a,*,2]

[a] Department of Endocrinology and Metabolism, Guangdong Provincial Key Laboratory of Diabetology, The Third Affiliated Hospital of Sun Yat-sen University, No. 600 Tianhe Road, Guangzhou, Guangdong 510630, China
[b] Department of Endocrinology and Metabolism, The First Affiliated Hospital of Shantou University Medical College, Shantou, Guangdong, China
[c] Department of Endocrinology and Metabolism, Guangdong Provincial People's Hospital, Guangzhou, Guangdong, China
[d] Department of Endocrinology and Metabolism, Zhujiang Hospital, Southern Medical University, Guangzhou, Guangdong, China

ARTICLE INFO

Article history:
Received 17 February 2016
Accepted 11 April 2016
Available online 14 April 2016

Keywords:
Cardiovascular autonomic neuropathy
Glycemic variability
Type 2 diabetes mellitus

ABSTRACT

Background: The relationship between glycemic variability, another component of glycemic disorders as well as chronic sustained hyperglycemia, and cardiovascular autonomic neuropathy (CAN) has not been clarified. Our aim is to investigate the association between glycemic variability and CAN in newly diagnosed type 2 diabetic patients.

Methods: Ewing tests were performed in 90 newly diagnosed type 2 diabetic patients and 37 participants with normal glucose tolerance as control from May 1, 2009, through September 30, 2010. According to the scores from Ewing tests, diabetic patients were divided into two groups: without CAN (CAN−) and with CAN (CAN+). All participants underwent a 48-h to 72-h continuous glucose monitoring (CGM). Coefficient of variability of glycemia (%CV), mean amplitude of glycemic excursions (MAGE) and means of daily differences (MODD) were calculated with the CGM data.

Results: The prevalence of CAN in patients with newly diagnosed type 2 diabetes was 22.2%. An increasing trend of glycemic variability was found from control group, CAN− group to CAN+ group. MAGE in CAN+ group was significantly higher than that in CAN− group (5.27 ± 1.99 mmol/L vs. 4.04 ± 1.39 mmol/L, $P = 0.001$). In the Logistic regression analysis, a significant relationship was shown between MAGE and CAN [odds ratio (OR): 1.73, 95% confidence interval (CI): 1.01–2.73, $P = 0.018$)]. The area under the receiver-operating characteristic curve for MAGE was superior to those for other dysglycemic indices in detecting CAN.

Conclusions: Glycemic variability is associated with CAN in patients with newly diagnosed type 2 diabetes. Among the glycemic variability indices, MAGE is a significant indicator for detecting CAN.

1. Introduction

Cardiovascular autonomic neuropathy (CAN) is one of the common diabetes-related complications, which is ultimately clinically important because of its correlation with increased cardiovascular mortality, all-cause mortality and reduced quality of life in diabetic patients [1].

It has been well demonstrated that autonomic neuropathy increases and progresses with the duration of diabetes [2]. Well control of risk factors of CAN at the early stage of diabetes can reduce the prevalence of CAN or even reverse its nature course [3,4]. Therefore, identification of risk factors of CAN in patients with newly diagnosed type 2 diabetes mellitus is of great clinical significance. However, the risk factors of CAN in type 2 diabetes mellitus are not completely clarified. Age, obesity, smoking, hyperinsulinemia, hypertension, hyperglycemia and duration of diabetes have been shown to be the main risk factors [5]. Among which, chronic sustained hyperglycemia is considered to be a pivotal pathophysiological factor in the development of CAN [6]. In recent years, glycemic variability, an important component of glycemic disorders in addition to chronic sustained hyperglycemia [7], has been indicated to be an independent predictor or risk factor of macro- and micro-vascular complications in diabetes [8]. Moreover, it is suggested that glycemic variability is correlated with peripheral neuropathy [9]. Considering that both peripheral neuropathy and CAN are nerve system disorders, and a clear relationship between diabetic peripheral neuropathy and CAN is well demonstrated [10], it is highly possible that glycemic variability, in addition to absolute hyperglycemia, might be a potential risk factor partly accounting for CAN in diabetic patients.

* Corresponding author.
E-mail address: wjianp@mail.sysu.edu.cn (J. Weng).
[1] These authors contributed equally to the paper.
[2] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2016.04.078
0167-5273/

To date, no study investigates the role of glycemic variability in CAN, especially in early course of diabetes. Hence, this study was designed to reveal the association between glycemic variability and CAN in drug naïve patients with newly diagnosed type 2 diabetes mellitus.

2. Methods

2.1. Subjects

The participants in this study were enrolled from four university affiliated hospitals in Guangdong Province, China between May 1, 2009 and September 30, 2010. A total of 90 patients with newly diagnosed type 2 diabetes mellitus, who had not received previous antihyperglycemic therapy, were enrolled as the diabetes group. Those who had stroke, congestive heart failure, cardiac arrhythmias, uncontrolled hypertension, severe liver insufficiency or renal insufficiency, proliferative retinopathy, psychiatric disease, anemia and alcohol, cigarette or coffee addiction were excluded. Patients were also excluded if they were pregnant, on β-blocker or digitalis treatment within a month. Forty participants with normal blood pressure [defined as systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DBP) <90 mmHg at rest] and normal glucose tolerance (NGT) confirmed by an oral glucose tolerance test were recruited as control group. The protocol was approved by the ethics committee of the Third Affiliated Hospital of Sun Yat-sen University. All subjects provided written informed consent before participation.

2.2. Measurements

After a 10-h overnight fast, anthropometric data were collected. Waist circumstance was measured at the midpoint between the lowest rib and the liac crest. Hip circumstance was measured as maximum circumference over the greater trochanters. Waist-to-hip ratio (WHR) was calculated as the waist circumstance divided by hip circumstance. Body mass index (BMI) was calculated as the weight (kg) divided by height squared (m^2). The mean value of the two consecutive blood pressure measurements 10 min apart in the sitting position was recorded as blood pressure level. Hypertension was defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg, or on anti-hypertension drugs prior to enrollment. Blood samples were collected before and 2 h after a fixed breakfast for measurements of Hemoglobin A1c (HbA1c), fasting lipid profiles, fasting and 2 h postprandial plasma glucose (FPG, 2hPG).

2.3. Assessment of glycemic variability indices

All subjects underwent a 48-h to 72-h continuous glucose monitoring (CGM) with the CGM Minimed System (CGMS; Medtronic, Northridge, CA). At least 4 times of capillary blood glucose monitoring per day were conducted to each subject during CGM period and entered into the CGMS monitor for calibration. After completion of CGM, the CGMS data was downloaded by the same investigator using CGMS 3.0C Solutions Software (Minimed, Medtronic). All glycemic variability indices obtained from CGMS were calculated after excluding the initial 2-h data of monitoring, which is considered to be the unstable calibration data. Glycemic variability indices adopted in this study included [11]: 1) Coefficient of variability of glycemia [%CV: standard deviation of blood glucose (SDBG) /mean blood glucose × 100]; 2) the mean amplitude of glycemic excursions (MAGE): the arithmetic mean of the differences between consecutive peaks and nadirs with measurement in the peak-to-nadir direction by the first qualifying excursion; 3) absolute means of daily differences (MODD): the mean of absolute differences between glucose values at the same time on two consecutive days.

2.4. Assessment of CAN

The standard battery of Ewing tests [12] used in this study included the Valsalva maneuver (Valsalva ratio), the deep breathing test of expiration-to-inspiration ratio (E/I), the lying to standing test (30:15 test) among the heart rate tests, and the orthostatic hypotension test. The orthostatic hypotension test was used to indentify sympathetic nerve dysfunction, while the other three to identify parasympathetic nerve dysfunction. Subjects were refrained from smoking and drinking coffee, wine and tea for at least 24 h before the tests. All subjects, including the diabetes group and the control group, were examined with the Ewing tests by well-trained investigators who were blind to the participant's laboratory results and CGMS data at each site. The tests were performed in a quiet room with temperature adjusted to 23–25 °C during 8:30 am to 4:00 pm (at least 2 h after breakfast). The detailed process was provided in Table 1. Each of the Ewing tests was performed twice, using the mean value of the results for analysis. A 5-min rest between each test was requested.

The severity of CAN was graded as follows: each test of Ewing tests was graded as normal (score = 0), borderline (score = 0.5), or abnormal (score = 1) (Table 2). The total score obtained from each test was calculated. Subjects with the total score ≥2 were diagnosed with CAN. Based on the total scores, diabetic patients were then further divided into two sub-groups: without CAN (CAN−) and with CAN (CAN+). In order to eliminate the confounding effect, subjects with a total score ≥2 in the control group were excluded in the further analysis.

2.5. Statistical analysis

Normally distributed continuous variables were presented as mean (SD). Differences between the diabetes group and control group were assessed by unpaired t-tests. Pairwise comparisons were conducted using the Least Significant Difference (LSD)-t test to analyze differences among the CAN+, CAN− and control groups. Multivariate analysis was performed with CAN as the dependent variable, glycemic variability indices and HbA1c as the independent variables to identify the relative risk of the glycemic indices for CAN, expressed as odds ratios (OR) with 95% confidence intervals (CI). Receiver-operating characteristic (ROC) curve was used to detect CAN with glycemic indices in type 2 diabetes mellitus. All statistical analyses were conducted with SPSS18.0 (IBM, Armonk, New York, United States). Significance was defined as $P < 0.05$.

3. Results

3.1. Prevalence of cardiovascular autonomic neuropathy

Three of 40 subjects with a total score ≥2 in the control group were excluded as predefined. Twenty out of 90 subjects in diabetes group (22.2%) have a total score ≥2 and classified as with CAN (CAN+), and the remaining as without CAN (CAN−). In the diabetes group, proportion of patients with abnormal sympathetic nerve function (diagnosed by score from orthostatic hypotension test) was much lower than those diagnosed with abnormal parasympathetic nerve function (diagnosed by scores from Valsalva ratio test, E/I test, or 30:15 test) (1.1% vs. 32.2%, 33.3%, 10%, respectively, $P < 0.001$).

3.2. Anthropometric and laboratory characteristics of subjects

Anthropometric and laboratory characteristics of the participants were shown in Table 3. Compared with those in the control group, patients in the CAN+ group were older ($P = 0.001$), had higher WHR ($P = 0.02$), higher heart rate ($P = 0.01$); CAN− group had higher WHR ($P = 0.006$), higher heart rate ($P = 0.01$), higher blood pressure ($P = 0.003$ for SBP; $P = 0.02$ for DBP, respectively), but lower high-density lipoprotein cholesterol (HDL-C) ($P = 0.01$). In the diabetes